National Children's Study

I. Proposed Core Hypothesis / Question

The development of beta cell and other autoantibodies, which subsequently increases risk for type 1 diabetes and other autoimmune disorders, occurs early during childhood, and is due to one or more environmental exposures among children who are genetically susceptible.

II. Workgroup

Gene-Environment Interactions

III. Contact Person for Proposed Hypothesis

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IV. Public Health Significance

Type 1 diabetes is one of the most common chronic diseases in children, with prevalence rates approximating 2 per 1000 in the US. The incidence of the disorder has been increasing in the Americas in around the world for the past decade (1). However, the etiology of type 1 diabetes remains unclear.

Epidemiologic patterns, including the dramatic geographic variations in type 1 diabetes incidence rates, variation in risk by ethnicity, the peak age at onset at puberty, and the more frequent diagnosis of the disease during the cold winter months, suggest that viruses, nutrition and socieconomic factors are involved (2). Potential environmental risk factors have been investigated in numerous populations, but the studies have yielded conflicting results. This has been due, in part, to a failure to account for disease susceptibility genes. Although genome screens found evidence of linkage to 15+ potential genes, the primary locus of susceptibility (*IDDM1*) is located in the HLA region of chromosome 6 (3,4). Estimated relative (odds ratios range from 10 - 100) and absolute risks (~3 - 6% through age 20 years) associated with high risk HLA genotypes have been studied in many populations (5).

Although lifelong insulin therapy is the only treatment for type 1 diabetes, there are currently several large clinical trials designed to evaluate a variety of approaches for primary (i.e., avoidance of cow's milk formula) and secondary disease prevention (i.e, high doses of nicotinamide, oral / nasal insulin) (6). Newborns, children and young adults who have a first degree relative with type 1 diabetes are currently being screened for early pre-clinical markers (i.e., beta cell autoantibodies) and / or high risk HLA susceptibility alleles. Those who are positive are eligible for randomization.

However, approximately 90% of the individuals who develop type 1 diabetes have no family history of the disease and are not eligible for these trials (7). Thus, for the public health impact of any of these interventions to be realized, they must be based on the general population and not high risk family members. As a result, several natural history studies are now following newborns who screen positive for high risk HLA susceptibility alleles (8,9). However, only one-half of the children who eventually develop type 1

diabetes carry these genes. Thus, approximately half of the remaining future incident cases will occur among those who screen negative for high risk HLA genotypes. These individuals are being excluded from follow-up.

The National Children's Study offers an unprecedented opportunity to complement the ongoing investigations of high risk children by evaluating a range of different disease susceptibility genes and environmental exposures. For example, there is considerable evidence to suggest that the contribution of HLA susceptibility alleles varies by age (10). The largest relative and absolute risk estimates for children who carry high risk genotypes are strongest for the youngest children (less than age 5 years). The contribution of the same genotypes is much less dramatic among children with an older age at onset (> 10 years). This suggests that around the time of puberty, loci other than those in the HLA region and / or environmental exposures may play a more important etiologic role. Thus, the evaluation of gene-environmental interactions in the development of type 1 diabetes must be evaluated among children with and without high risk HLA susceptibility alleles. At present, there is such investigation. This evaluation could be conducted as part of the National Children's Study, and would address hypotheses that are not be tested by the ongoing studies of type 1 diabetes.

a. Incidence

Annual age-adjusted incidence ranges from over 40 / 100,000 per year in Finland to less than 1 / 100,000 per year in China for children age 0 -14 years (11). Rates in the US are moderate (~20 / 100,000 per year). However, the incidence is increasing worldwide at an estimated rate of 3% per year (1). These changes are particularly striking among young children (less than age 5 years) and in the ethnic minorities.

b. Morbidity

Although the prognosis associated with type 1 diabetes has improved dramatically in recent decades, affected individuals remain at high risk for premature morbidity (12) and mortality (13) from cardiovascular, cerebrovascular and peripheral vascular diseases. Moreover, type 1 diabetes is associated with retinopathy and nephropathy, which are the leading causes of blindness and renal failure, respectively, among young adults

c. Quality of Life

In addition to having higher rates of disability than non-diabetic persons of similar age (14), the impact of diabetes may also be felt in ways that are less easily quantifiable. The presence of type 1 diabetes is known to influence the insurance and employment experiences of affected individuals. Health, life and sometimes automobile insurance are generally more difficult to obtain for persons with type 1 diabetes (15). Affected individuals may also face discrimination in the job application process, as well as limitations in the types of jobs available to them (16). Employment in commercial driving, for example, is restricted due to concern regarding potential hypoglycemia (17).

d. Mortality

Beginning in childhood, the mortality experience for persons with type 1 diabetes is significantly poorer for unaffected persons of the same age (13). This becomes particularly striking in the early adult years. More than one-half of the deaths that currently occur among affected individuals ages 25 - 40 years are due to vascular disorders (18). This represents an approximate 20-fold increased risk compared with the rates for non-diabetic individuals in this age group. Although this may be related to metabolic disturbances (e.g., hyperglycemia, hypertension, etc.), such abnormalities are

unlikely to explain the magnitude of the increased mortality associated with type 1 diabetes.

e. Cost

Studies that describe the economic costs of diabetes often consider the direct or medical costs of the disease. Less frequently, the indirect costs of diabetes are evaluated. Examples of indirect costs include the value assigned to morbidity, disability and premature mortality associated with type 1 diabetes. From an economic perspective, the most important medical costs relate to the daily management of the disease and the treatment of late-stage complications. The annual costs of type 1 diabetes typically range between $1500 per person for the standard insulin regimens, to nearly $6000 for insulin pump protocols (19). Out-of-pocket health care costs for families with type 1 diabetes in the US typically exceed $1000 per year (20). These costs increase substantially after the development of long-term complications.

f. Perceived Importance

In addition to the long-term complications of type 1 diabetes, affected individuals and their family members are likely to develop other autoimmune disorders, such as Celiac disease (21) and Hashimoto's thyroiditis (22). This suggests that similar genetic and / or environmental factors may be involved in the development of a general autoimmune phenotype. It has been further suggested that these same risk factors may be related to other alterations in immune function, such as those associated with asthma. Childhood asthma is also a priority of the National Children's Study. Thus, by studying the development of autoimmunity, one is likely to identify risk factors that also contribute to the development of other chronic diseases in children. And concurrent investigations, such as those of childhood asthma are likely to expand our understanding of type 1 diabetes and other autoimmune diseases.

V. Justification for a Large, Prospective, Longitudinal Study

See above.

VI. Scientific Merit

See above.

VII. Potential for Innovative Research

Because there are several prospective investigations among children at high risk for developing type 1 diabetes, it is suggested at a thorough review of the literature published during the past decade warranted. From the perspective of the National Children's Study, these investigations would provide 'pilot data' for the current proposal. It should be emphasized that the proposed investigation would not duplicate, but rather complement currently funded investigation for reasons described above.

It is also suggested that a meeting between the investigators involved research regarding the etiology and epidemiology of type 1 diabetes and key members of the National Children's Study advisory groups be planned. Presentations and discussions at these meeting would provide important information regarding design and protocol development for testing the proposed hypothesis.

VIII. Feasibility

a. Critical Period for Exposure and Outcome

This is likely to begin during the prenatal period, and related to maternal illnesses, infant and childhood nutrition, etc. For example, several studies have shown that children born to mothers' who had enteroviral infections during pregnancy had a higher risk of developing type 1 diabetes. Other reported risk factors include exposure to cow's milk formula during the first three months of life, childhood infections, etc. Because the peak age at onset is at puberty, the exposures that increase type 1 diabetes risk must occur early in life.

b. Sampling Needs

Case - parent trios may be considered as a possible sampling unit.

c. Contact

This should not require additional testing other than that which is currently planned for the National Children's Study.

d. Nature of Measurement

Suggested measures relate to evaluations of autoantibodies, genetic markers, exposures to viruses and pesticides, infant / childhood nutrition, quality of drinking water, etc.

e. Burden on the Participant and Family

It is anticipated that this aspect of the National Children's Study pose no additional burden to the participant and family.

f. Ethical Considerations

Appropriate strategies for the collection and storage of biological samples need to be determined. Other potential concerns relate to psychosocial issues that may arise when a child participants in a long term prospective study. These include concerns for the child, as well as the impact on family dynamics, etc., which will be addressed in planning for the National Children's Study.

IX. References

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